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GENETIC EPIDEMIOLOGY

Exercise participation and self-rated health: Do common genes explain the association?

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Abstract. The purpose of this study is to investigate whether there is an association between exercise participation and self-rated health and whether this association can be explained by common genes and/or common environmental influences. In a sample of 5,140 Dutch adult twins and their non-twin siblings from 2,831 families, exercise participation (sedentaries, light or moderate, vigorous exercisers) and self-rated health were assessed by survey. To investigate the etiology of the association, bivariate genetic models using structural equation modeling were applied to the data. The correlation between exercise participation and self-rated health is significant but modest ($r = 0.20$). Exercise participation and self-rated health are both heritable (around 50% of the

variance of both phenotypes is explained by genetic factors). The genetic factors influencing exercise participation and self-rated health partially overlap ($r = 0.36$) and this overlap fully explains their phenotypic correlation. We conclude that the association between exercise and self-rated health can be explained by genes predisposing to both exercise participation and self-rated health. These genes may directly influence both phenotypes (pleiotropy). Alternatively, genes that affect exercise or self-rated health may indirectly influence the other phenotype through a causal relationship. We propose that identification of the genes that cause differences in exercise behavior will help resolve the issue of causality.

Key words: Causality, Exercise, Genetics, Heritability, Self-rated health, Twins

Introduction

In the last decades it has become increasingly clear that persistent regular exercise during adulthood protects from both physical health problems (i.e., cardiovascular disease) and mental health problems (i.e., anxiety and depression) [1–3]. Not surprisingly, some studies also report an association between exercise participation and self-rated health [4–7]. People who do not participate in exercise at a regular basis are more likely to evaluate their health as poor. Self-rated health can be described as a general self-evaluation of a person's health, reflecting both physical and mental aspects of health [8, 9]. Studies show that self-rated health measured with a single question is a very good predictor of morbidity and mortality [8, 10]. An additional advantage of the self-rated health measure is that it is easy to include in large-scale epidemiological survey studies at relatively low costs.

If the overall judgment of a person's health is negative this might be one of the causes of a sedentary lifestyle. On the other hand, a sedentary lifestyle could also cause a poor rated health, because a sedentary lifestyle increases the risk for true physical and/or mental health problems. These explanations

are not mutually exclusive, in that there may also be a reciprocal causal relationship between exercise and self-rated health. Perceived lowering of health may reduce exercise frequency which in turn may further influence the perception of health. Although often overlooked, the association between exercise and self-rated health could also be explained by a third underlying variable, such as common genetic or environmental factors that predispose to a sedentary lifestyle as well as poor self-rated health. It is, for instance, well-known that individual differences in adult exercise behavior are heritable [5, 11–13] and there is increasing evidence that individual differences in self-rated health may also be heritable [14, 15]. Hence, a common set of genes may influence both traits (pleiotropy).

As far as we know, there exists only one study that investigated the etiology of the association between exercise participation and self-rated health using a genetic approach [5]. In a small sample of 300 male twin pairs aged 35–70 years, lifetime exercise and self-rated health were significantly related (odds ratio 1.62) and this association could fully be explained by the overlap of genetic factors influencing both phenotypes. It is not known, however, whether these results also hold for females and younger adults.

The purpose of the present study, using structural equation modeling techniques, is to investigate (1) whether there is an association between exercise participation and self-rated health in a large sample of young and middle-aged twins and their siblings and (2) whether the association between exercise participation and self-rated health can be explained by common genes, other familial factors (i.e., shared environmental influences) or unique environmental factors.

Methods

Subjects

This study is part of an on-going study on lifestyle and health in twin families that are voluntarily registered with the Netherlands Twin Registry (NTR) [16]. Since 1991, every two to three years participants receive questionnaires on lifestyle and health (i.e., health status, exercise participation, smoking behavior, alcohol use, and personality). In this study, we focus on data on exercise participation and self-rated health obtained from twins and their siblings collected in 2002. In total, 5,950 twins and siblings participated in the 2002 survey. Twins and siblings aged 18–50 years were selected ($n = 5,200$). We excluded twins with unknown zygosity ($n = 23$), subjects for whom both data on exercise participation and self-rated health was missing ($n = 3$) and genetically unrelated and half siblings ($n = 25$). In large families, only the first two brothers and the first two sisters of a twin pair were selected. This excluded 4 brothers and 5 sisters from large families. The final sample consisted of 5,140 twins and siblings from 2,831 families. There were 3,950 twins, 465 brothers and 725 sisters. There were 1,370 complete and 1,210 incomplete twin pairs. Complete twin pairs are pairs where measurements are available for both twins, whereas in incomplete twin pairs data are available for only one twin. Data from incomplete pairs were retained in the analyses to improve the estimation of the prevalences.

Zygosity of same-sex twins was determined by DNA typing for 27.5% of the same-sex twin pairs [17]. For the other same-sex twin pairs zygosity was based on eight items on physical similarity and the frequency of confusion of the twins by parents, other family members and strangers. Agreement between zygosity based on these items and zygosity based on DNA was 97%. There were 366 monozygotic male (MZM), 223 dizygotic male (DZM), 859 monozygotic female (MZF), 493 dizygotic female (DZF) and 639 dizygotic opposite-sex (DOS) twin pairs (both complete and incomplete twin pairs). Sex and age of the participants was always known, exercise participation was missing for 16 participants (0.3%) and self-rated health was missing for 63 participants

(1.2%). The mean age of all participants was 30.5 (SD = 7.0).

Measures

Exercise participation was assessed with multiple questions. Firstly, the question ‘Do you exercise regularly?’ (Yes or No) was asked. If the answer was affirmative, further information on type of exercise, frequency and duration was gathered. MET scores (Metabolic equivalents) were assigned to the different types of sports using the Ainsworth’s Compendium of physical activity [18]. One MET equals the rate of energy expended when at rest (1 kcal/kg/h). The respondents were classified in three distinct ordered categories. The first category consists of respondents who did not participate in sports (i.e. no MET-score could be assigned); these respondents were classified as sedentary. The second category consists of light and moderate exercisers. Light and moderate exercisers are respondents who are involved in some type of exercise but who do not meet the criterion for vigorous exercise (exercising at least 60 min weekly, two or more times a week, with an intensity of 6 METs or higher). The third category consists of respondents who meet the above criterion for vigorous exercise. The resulting measure of exercise participation (three categories: sedentaries, light or moderate exercisers and vigorous exercisers) was used in the analyses.

Self-rated health was assessed with the single question ‘How, in general, is your health?’ [9]. Participants could respond with Bad, Poor, Fair, Good or Excellent. Because the prevalences of self-reported bad, poor or fair health were low, the data from the first three and the last two categories were pooled together. This resulted in a measure of self-rated health with two categories defined as Less than good and Good/Excellent health.

Statistical analyses

Structural equation modeling was used to estimate the correlation between exercise and self-rated health, the relative contribution of genetic factors to variation in exercise participation and self-rated health (i.e., the heritability), and the overlap between genetic and environmental factors that influence the two traits. Threshold models were fitted to the raw ordinal data using the software package Mx [19]. The threshold model assumes that a categorical variable has an underlying liability with a continuous and standard normal distribution. Thresholds divide the liability distribution into discrete categories (e.g. ‘Less than good health’ and ‘Good/Excellent health’). The thresholds are based on the prevalence of the different categories in the population. The resemblances between relatives for the liabilities of exercise

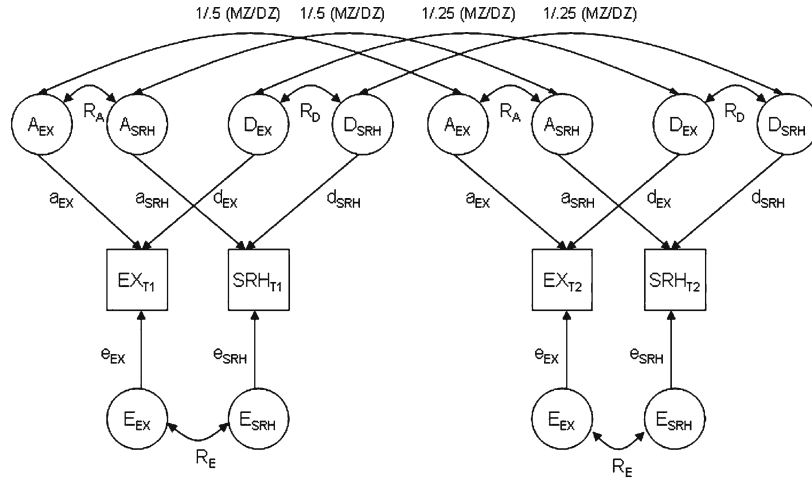


Figure 1. Bivariate ADE model for exercise participation and self-rated health. EX_{T1} : Exercise participation of twin 1; SRH_{T1} : Self-rated health of twin 1; EX_{T2} : Exercise participation of twin 2; SRH_{T2} : Self-rated health of twin 2; A_{EX} : Additive genetic factor for exercise participation; A_{SRH} : Additive genetic factor specific for self-rated health; D_{EX} : Non-additive genetic factor for exercise participation; D_{SRH} : Non-additive genetic factor for self-rated health; E_{EX} : Unique environmental factor for exercise participation; E_{SRH} : Unique environmental factor for self-rated health; a_{EX} : Square root of the proportion of variance due to A of exercise participation; a_{SRH} : Square root of the proportion of variance due to A of self-rated health; d_{EX} : Square root of the proportion of variance due to D of exercise participation; d_{SRH} : Square root of the proportion of variance due to D of self-rated health; e_{EX} : Square root of the proportion of variance due to E of exercise participation; e_{SRH} : Square root of the proportion of variance due to E of self-rated health; R_A : Additive genetic correlation between exercise participation and self-rated health; R_D : Non-additive genetic correlation between exercise participation and self-rated health. R_E : Unique environmental correlation between exercise participation and self-rated health.

and self-rated health are estimated with polychoric correlations.

The comparison of monozygotic (MZ) and dizygotic (DZ) twin correlations is a first step in evaluating the relative influences of genetic and environmental factors on variation in a trait. MZ twin pairs have all, or nearly all, genes in common. DZ twin pairs and siblings, share on average only half of their segregating genes. If the MZ correlation is higher than the DZ/sib correlation, genetic influences are implicated. If the DZ correlation is higher than half the MZ correlation, there is evidence for common environmental effects (C) shared by family members. If MZ correlations are lower than 1, this implies that unique environmental effects (E) play a role. Unique environmental effects are those environmental effects that are not shared between family members. Genetic effects can be additive (A); (the summation of effects of multiple alleles at different loci) or can act in a non-additive manner. Non-additive genetic effects, or dominance (D), occur when there is interaction between alleles within a locus or across loci (epistasis). MZ twin pairs share all additive genetic, non-additive genetic and shared environmental effects, whereas DZ twin pairs and full siblings share on average half of their additive genetic effects, a quarter of their non-additive effects and all shared environmental effects. The effects of C and D cannot be estimated simultaneously from data from twins and siblings and a choice for an ADE or ACE model has to be made based on the pattern of MZ–DZ

correlations (C will make these correlations more alike, D will make them more different from each other).

The comparison of cross-twin cross-trait correlations provides information on the etiology of the *association* between exercise participation and self-rated health. If the cross-twin cross-trait correlations are larger than zero, this suggests that the etiology of the correlation between exercise and self-rated health is familial. If the MZ cross-twin cross-trait correlation is larger than the DZ cross-correlation, this suggests that common genetic factors explain the correlation. If the MZ cross-twin cross-trait correlation equals the DZ cross-correlation, common shared environmental factors account for the correlation. Data from siblings were added to the design to increase the power to detect possible additive and non-additive genetic and shared environmental influences [20]. Correlations for DZ twins, twin-sibling pairs and sibling-sibling pairs have the same expectations, because all those pairs share on average 50% of their genes and are brought up in the same family. Therefore, in subsequent models, non-twin siblings are treated as DZ twins.

A number of different models were fitted to the data and their fit was compared by means of the log-likelihood ratio test (LRT). The difference in minus two times the log-likelihood ($-2LL$) between two nested models has a χ^2 distribution and the degrees of freedom (df) equals the difference in df between the two models. If the χ^2 -test yielded a p -value higher

Table 1. Twin and cross-twin cross-trait correlations for exercise participation and self-rated health

	MZM	DZM*	MZF	DZF*	DOS*	MZ	DZ*
Twin correlations for exercise participation							
R	0.59	0.25	0.55	0.28	0.21	0.56	0.24
CI	0.45; 0.69	0.11; 0.38	0.46; 0.62	0.19; 0.36	0.13; 0.28	0.49; 0.62	0.19; 0.29
N	203	352	552	911	1,043	755	2,306
Twin correlations for self-rated health							
R	0.64	0.03	0.58	0.19	0.24	0.58	0.19
CI	0.02; 0.91	-0.28; 0.38	0.42; 0.72	-0.00; 0.38	0.05; 0.41	0.43; 0.72	0.07; 0.31
N	201	346	540	898	1,021	741	2,265
Cross-twin cross-trait correlations for exercise participation and self-rated health							
R	0.08	0.13	0.15	0.13	0.03	0.15	0.08
CI	-0.22; 0.32	-0.04; 0.29	0.05; 0.24	0.04; 0.23	-0.07; 0.11	0.05; 0.23	0.02; 0.14
N	404	699	1,092	1,808	2,064	1,496	4,571

R: Polychoric correlations; CI: 95% confidence interval; N: Number of twin pairs; MZM: Monozygotic male twin pairs; DZM: Dizygotic male twin pairs; MZF: Monozygotic female twin pairs; DZF: Dizygotic female twin pairs; DOS: Dizygotic opposite sex twin pairs; MZ: Monozygotic twin pairs pooled over sex; DZ: Dizygotic twin pairs pooled over sex.

* Note that DZ pairs also include siblings.

than 0.01 the fit of the constrained model was not significantly worse than the fit of the more complex model and the constrained model was kept as the most parsimonious and best fitting model.

Firstly, in a bivariate saturated model, the thresholds, the correlation between traits, the twin correlations and the cross-twin cross-trait correlations were estimated. We tested for sex and zygosity effects on the thresholds and the correlations. Secondly, we fitted a series of genetic models. We started with an ADE model or an ACE model. The bivariate ADE model for exercise participation and self-rated health is depicted in Figure 1. In the ADE model, there are 7 free parameters (the proportions of variance due to A of both traits, the proportions of variance due to D of both traits and the additive genetic, non-additive genetic and unique environmental correlations). The proportions of variance due to E for both traits are not free parameters, since the total variance of the liability distribution is fixed at 1. Next, an AE model was fitted to the data (with 4 free parameters: two heritabilities, an additive genetic and a unique environmental correlation) to test the significance of D (or C). Finally, we fitted a model with the genetic correlation fixed at zero (3 free parameters), a model with the unique environmental correlation fixed at zero (3 free parameters) and a model with both correlations at zero (2 free parameters) to test their significance. In all these bivariate genetic models, three thresholds were estimated (2 for exercise participation and 1 for self-rated health).

Results

The prevalence of no, light/moderate or vigorous exercise participation (represented by the thresholds in the saturated model) was different in males and

females ($\chi^2 = 65.084$, $\Delta df = 4$, $p < 0.001$), but not different between MZ and DZ twins ($\chi^2 = 9.022$, $\Delta df = 4$, $p = 0.061$). As much as 39% of the sample is not involved in any kind of exercise, 44% exercises at a light to moderate level and only 17% is regularly participating in vigorous exercise activities. The sex difference in exercise participation is found in the percentage of vigorous exercisers: 23% of the males are involved in regular vigorous exercise activities, compared with 14% of the females. The prevalence of self-rated health was not significantly different between MZ and DZ pairs ($\chi^2 = 8.102$, $\Delta df = 2$, $p = 0.017$), but females reported more often less than good health (12%) than males (7%) ($\chi^2 = 37.545$, $\Delta df = 2$, $p < 0.001$).

The correlation between exercise participation and self-rated health was 0.20 (95% CI: 0.15–0.22) and did not significantly differ for males and females ($\chi^2 = 1.424$, $\Delta df = 1$, $p = 0.233$). The estimates of the twin correlations for exercise participation and self-rated health and the cross-twin cross-trait correlations are presented in Table 1. The twin correlations of exercise participation were equal in males and females ($\chi^2 = 2.021$, $\Delta df = 3$, $p = 0.568$). MZ twin correlations were significantly larger than DZ correlations ($\chi^2 = 33.840$, $\Delta df = 2$, $p < 0.001$). The twin correlations of self-rated health were equal in males and females ($\chi^2 = 1.213$, $\Delta df = 3$, $p = 0.750$). MZ correlations were significantly larger than the DZ correlations ($\chi^2 = 12.721$, $\Delta df = 2$, $p = 0.002$). There were no significant differences across sex in the cross-correlations ($\chi^2 = 3.636$, $\Delta df = 3$, $p = 0.304$). The twin correlations for exercise and self-rated health suggest that additive and non-additive genetic factors play a role. Therefore, we next fitted an ADE model.

The results of the tests for the significance D and the genetic and environmental correlations are given in Table 2. The most parsimonious and best fitting

Table 2. Bivariate model fitting results and parameter estimates for exercise participation and self-rated health

Model fitting results							Parameter estimates								
							Exercise participation			Self-rated health					
Model	vs.	−2LL	df	χ^2	Δ df	p	a^2	d^2	e^2	a^2	d^2	e^2	R_A	R_D	R_E
1. Saturated	—	13462.72	10172	—	—	—	—	—	—	—	—	—	—	—	—
2. ADE	1	13472.13	10184	9.31	12	0.68	39.3	16.9	43.8	26.9	31.0	42.2	0.67	−0.31	0.13
3. AE, R_A R_E	1	13475.41	10187	12.59	15	0.63	54.1	—	—	53.5	—	—	0.30	—	0.10
4. AE, R_E	3	13490.26	10188	14.85	1	<0.01	52.8	—	—	50.8	—	—	—	—	0.00
5. AE, R_A	3	13476.75	10188	1.34	1	0.25	54.4	—	45.6	53.8	—	46.2	0.36	—	—
6. AE	3	13529.09	10189	53.68	2	<0.01	54.1	—	—	54.8	—	—	—	—	—

Bold: Most parsimonious and best fitting model.

vs.: versus; −2LL: −2 log-likelihood; df: degrees of freedom; χ^2 : chi-square test statistic; Δ df: degrees of freedom of χ^2 test; p : p -value; a^2 : proportion of variance due to additive genetic factors of exercise participation/self-rated health; d^2 : proportion of variance due to non-additive genetic factors of exercise participation/self-rated health; e^2 : proportion of variance due to unique environmental factors of exercise participation/self-rated health; R_A : additive genetic correlation; R_D : non-additive genetic correlation; R_E : unique environmental correlation.

model is an AE model with a genetic correlation but no environmental correlation. In this model, 54.4% (95% CI: 47.9–58.3) of the variance in liability of exercise participation is explained by additive genetic factors. The remaining 45.6% (95% CI: 40.0–52.0) is entirely explained by unique environmental factors. For self-rated health, 53.8% (95% CI: 39.4–66.1) of the variance in liability of self-rated health is explained by additive genetic factors and 46.2% by unique environmental factors (95% CI: 43.0–60.6). The genetic correlation is 0.36, which means that the additive genetic factors influencing exercise participation and self-rated health show moderate overlap. These overlapping additive genetic factors explain the entire correlation between exercise participation and self-rated health (0.20); no contribution of the unique environment to this correlation is found.

Discussion

The main finding in this study is that exercise participation and self-rated health are modestly related ($r = 0.20$), and this association can be explained by a set of common genes predisposing to both exercise participation and self-rated health. Individual differences in both exercise participation (heritability 54.4%) and self-rated health (heritability 53.8%) are explained by genetic influences and unique environmental influences. The association between exercise participation and self-rated health can be fully explained by overlapping genetic factors.

The finding of a modest correlation between exercise and self-rated health is consistent with two other studies reporting a correlation of 0.20 in adults aged 18 years and older [6] and of 0.36 in elderly females [4]. Our finding that common genes account for the association between exercise participation and self-rated health is in line with the single previous study

that investigated the nature of this association in terms of common genetic and/or environmental influences [5]. They found that common genes accounted for the association between lifetime exercise and self-rated health in a small sample of 300 male twin pairs aging 35–70 years. The present study extends these findings by showing that common genes also explain the association between exercise participation and self-rated health in young adulthood and females.

The importance of common genetic influences on exercise participation and self-rated health in adulthood can be interpreted in different ways. A first scenario is that there is a set of genes that is expressed in different parts of the body (i.e., in muscle tissues, the brain or different organs) or that has different functions (i.e., the same genes coding for different proteins, or post-expression protein processing), which might independently cause individual differences in exercise behavior and individual differences in self-rated health. For example, a recent study [21] showed that genetic variation in the Angiotensin I-Converting Enzyme (ACE) gene, a gene known to have different functions, such as the regulation of blood pressure and cell growth, is also associated with physical activity. It is not unthinkable that a gene with such a diversity of body functions might also influence self-rated health, through its influence on physical and possibly also mental health.

On the other hand, our finding of a common genetic predisposition does *not* exclude the existence of causality between exercise and self-rated health. It could be, for example, that genes that directly influence exercise participation indirectly influence self-rated health, because exercise exerts a causal influence on self-rated health. In this second, causal, scenario, an individual's genetic predisposition to be sedentary might for instance cause a poor self-rated health. This may come about through an actual

decrease in physical health and well-being caused by a sedentary lifestyle, or because people weigh the absence of any exercise behavior in the evaluation of their health. In a third, reverse causal, scenario, genes influencing mental or physical health may also influence exercise behavior. If a person judges his or her health to be low, for instance, this is known to constitute a barrier for (continuation of) exercise behavior [22, 23].

A good future strategy to discriminate between these scenarios would be to identify the actual genetic variation influencing exercise participation. If the genetic variants associated with exercise behavior also influence self-rated health and do so independently of exercise behavior, that is the association is of comparable strength in sedentaries, moderate and vigorous exercisers, this argues in favor of genetic pleiotropy. If a causal mechanism is driving the association, for example when exercise causes improved self-rated health, the genetic variants associated with exercise behavior will no longer be associated with self-rated health when tested within the separate groups of sedentary, moderate and vigorous exercisers.

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